

### **Remarks**

Claims 26-43 are pending in the application. Claims 30-38 have been withdrawn from consideration. Claim 39 has been amended to include the recitation “wherein the  $\alpha$ -particle emitting radioisotope is  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ .” Support for this amendment can be found, for example, at page 7, ll. 17-19 and page 10, ll. 14-22. No new matter has been introduced. Applicant respectfully requests entry of the amendment.

### **Priority**

The Examiner asserts that the limitations in claims 26-29 only have support back to abandoned application 08/097,471, filed July 27, 1993, and therefore the Examiner has applied an intervening reference in the 35 USC 103(a) rejections discussed below. Applicant is still assessing the priority of claims 26-29, and therefore applicant responds to the intervening reference.

### **Claim Objections**

The Examiner objected to claim 39 because there was missing the term “comprising” or “consisting” between “radioconjugate” and “of.” The claim has been amended accordingly.

### **Rejections Under 35 U.S.C. §112**

The Examiner has rejected claims 39-43 under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner asserts that the phrase in claim 39, “radioconjugate of a targeting moiety bound, directly or indirectly, to an  $\alpha$ -particle emitting radioisotope,” is unclear as to whether the radioconjugate is bound to an  $\alpha$ -particle emitting radioisotope or whether the  $\alpha$ -particle emitting radioisotope is part of the radioconjugate. Applicant has amended claim 39 to

clarify that the  $\alpha$ -particle emitting radioisotope is part of the radioconjugate. Therefore, applicant requests withdrawal of this rejection.

### **Rejections Under 35 U.S.C. §102**

In § 8 of the Office Action, the Examiner has rejected claims 39-43 as anticipated by Subramanian (US 5,292,868) under 35 U.S.C. 102(b). In reply, applicant traverses the rejection. Applicant respectfully points out that Subramanian was published on March 8, 1994, and therefore is not valid 102(b) art. Further, it is not clear whether Subramanian is valid art under any section under 35 U.S.C. 102. Claims 39-43 have priority to USPN 5,246,691, which itself claims priority to June 19, 1989. To clarify that claims 39-43 have priority to USPN 5,246,691, applicant has amended claim 39 to specify that the  $\alpha$ -particle emitting radioisotope is  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . Accordingly, applicant requests the Examiner to reconsider and withdraw this ground of rejection.

In § 9 of the Office Action, the Examiner has rejected claims 39-40 and 42 as anticipated by Macklis (Science, vol. 240, pp. 1024-1026, 1988) under 35 U.S.C. 102(b). In reply, applicant traverses the rejection. Applicant has amended claim 39-43 to specify that the  $\alpha$ -particle emitting radioisotope is  $^{225}\text{Ac}$  or one of its daughters. Macklis does not disclose all of the elements of the claims. For example, Macklis only discloses  $^{212}\text{Bi}$  and therefore does not disclose the claim element " $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ ." Accordingly, applicant requests the Examiner to reconsider and withdraw this ground of rejection.

### **Rejections Under 35 U.S.C. §103**

In § 12 of the Office Action, the Examiner rejected claims 26 and 29 under 35 U.S.C. 103(a) as allegedly obvious over Subramanian in view of van Geel (USPN 5,355,394) and Kozak (Tibtech, vol. 4, no. 10, pp. 2590264 (1986)). Applicant traverses the rejection. First, the combination of Subramanian in view of van Geel and Kozak do not make obvious the claimed invention because the combination does not disclose all of the elements of the claims. For example, claims 26 and 29 both specify that the conjugate binds to target cells that are

micrometastases having a diameter of about 1 mm or less. Neither Subramanian, van Geel, nor Kozak disclose or suggest that radioconjugates can be used against such micrometastases. Further, claims 26 and 29 both specify a method comprising providing a sufficient quantity of  $^{225}\text{Ac}$  to produce a therapeutically effective amount of  $^{213}\text{Bi}$  through radioactive decay, binding the  $^{225}\text{Ac}$  onto a substrate for immobilizing  $^{225}\text{Ac}$ , eluting from the substrate  $^{213}\text{Bi}$  produced by bound  $^{225}\text{Ac}$ , coupling the eluted  $^{213}\text{Bi}$ , substantially free of  $^{225}\text{Ac}$ , to a targeting moiety to form a conjugate. The Examiner relies on Kozak to provide for the claim element of an immobilizing substrate for producing  $^{213}\text{Bi}$  from  $^{225}\text{Ac}$  (see Office Action page 6, 2nd full paragraph). However, Kozak is directed to obtaining  $^{212}\text{Bi}$  from decay of thorium-228 or radium-224. Kozak nowhere mentions that  $^{213}\text{Bi}$  can be obtained from  $^{225}\text{Ac}$ , nor is this disclosed implicitly because  $^{212}\text{Bi}$  cannot be obtained from  $^{225}\text{Ac}$ .

A suggestion or motivation to combine prior art references must implicitly or explicitly come from the references themselves or from the nature of the problem to be solved in order to prevent the picking and choosing among isolated disclosures in the prior art to deprecate the claimed invention. *Ecolchem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) (citing *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). There is no motivation to combine Subramanian with Kozak. Practitioners would not have been motivated to look to references like Kozak because Kozak teaches away from the claimed invention. For example, in Table 1, Kozak provides a list of "Radionuclides suitable for imaging and/or therapy." The list includes,  $^{111}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{67}\text{Ga}$ ,  $^{186}\text{Re}$ ,  $^{132}\text{I}$ ,  $^{131}\text{I}$ ,  $^{188}\text{Re}$ ,  $^{67}\text{Cu}$ ,  $^{109}\text{Pd}$ ,  $^{47}\text{Sc}$ ,  $^{90}\text{Y}$ ,  $^{211}\text{At}$ ,  $^{212}\text{Pb}$ ,  $^{212}\text{Bi}$ . Kozak nowhere discloses or suggests  $^{213}\text{Bi}$  or  $^{225}\text{Ac}$ .

Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 13 of the Office Action the Examiner rejects claim 26 as obvious over Macklis in view of van Geel and Kozak. Applicant traverses the rejection. First, this combination of art does not disclose all of the elements of claim 26. For example, the combination does not teach that radioconjugates can be used against micrometastases having a diameter of about 1 mm or

less. Further, as explained above, the combination does not disclose that  $^{213}\text{Bi}$  can be obtained from  $^{225}\text{Ac}$  because Kozak only discusses other radionuclides. There is also no motivation to combine the references because both Macklis and Kozak teach away from the invention in their use of  $^{212}\text{Bi}$ . In the attached copy of the Declaration under 37 CFR 1.132 of Dr. David Scheinberg (submitted in the Reexamination of USPNs 5,246,691 and 5,641,471, which the present application claims priority to; see also Declaration of Dr. Gansow), Dr. Scheinberg reflects upon the past state of the art that did not recognize the therapeutic utility of  $^{225}\text{Ac}$  and  $^{213}\text{Bi}$ . “[W]e had begun by 1980 to consider using alpha emitters for therapy, and for alpha emitters we and other investigators in the field focused on bismuth-212 with virtually all the efforts going forward with respect to bismuth-212; It was only after the urging of Dr. Geerlings that we and, later, after we presented our data showing utility, others in the field diverted our focus from bismuth-212 to actinium-225 and bismuth-213 as sources of alpha radiation for therapy.” Therefore, Applicant requests the Examiner reconsider and withdraw this ground of rejection.

In § 14 of the Office Action, the Examiner rejected claim 27 as unpatentable over Subramanian in view of van Geel, Kozak, and Greer (USPN 4,894,364). Applicant traverses the rejection. As discussed above, the combination of Subramanian, van Geel, and Kozak neither discloses all of the elements of the claims; nor is there a motivation to combine these references. Further, there is no motivation to combine Greer with any of the references. The Examiner cites Greer at col. 11, lines 59-66, to assert that it teaches administering repeated dosages with less total radiation to achieve effective tumor killing. However, Greer teaches away from the invention because it focuses on X-ray or gamma-ray therapies (see for example, col. 11, lines 37-40). This is in contrast to the present invention, which uses alpha-radiation, and teaches that gamma-radiation is not desired. “Due to the decay sequence which results mainly in  $\alpha$ - and/or  $\beta$ -radiation it has become possible that no protection against radiation is necessary. This is extremely useful, because due to the absence of gamma radiation it has become possible that the conjugation can be done at the bed side or in a nearby nuclear medicine lab without the necessity to apply radiation shielding or isolation of the patient or the equipment.” (See Application as

filed at page 8, ll. 17-27, emphasis added.) Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 15 of the Office Action, the Examiner rejected claim 27 as unpatentable over Macklis in view of van Geel, Kozak, and Greer (USPN 4,894,364). Applicant traverses the rejection. As discussed above, the combination of Macklis, van Geel, and Kozak neither discloses all of the elements of the claims; nor is there a motivation to combine these references. Both Macklis and Kozak teach away from the invention in their use of  $^{212}\text{Bi}$ . Further, there is no motivation to combine Greer with any of the references. Greer teaches away from the invention because it focuses on X-ray or gamma-ray therapies (see for example, col. 11, lines 37-40). This is in contrast to the present invention, which uses alpha-radiation, and teaches that gamma-radiation is not desired. Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 16 of the Office Action, the Examiner rejected claim 28 as unpatentable over Subramanian in view of van Geel, Kozak, and Turner (USPN 5,296,216). Applicant traverses the rejection. As discussed above, the combination of Subramanian, van Geel, and Kozak neither discloses all of the elements of the claims; nor is there a motivation to combine these references. Neither is there a motivation to combine Turner. Turner is directed to “a preparation adapted for prophylaxis and treatment of oral lesions.” (See col. 2, ll. 30-31.) The claimed formulations in Turner “include premixed forms of hydrogen peroxide and sodium bicarbonate.” (See col. 2, ll. 32-34.) The Examiner asserts that Turner teaches administering radiotherapy with continuous intravenous infusion to prevent recurrence of cancer, and cites Turner at col. 6, ll. 3-14. However, the radiotherapy reported by Turner at col. 6, ll. 3-14 is 5-fluorouracil. Turner nowhere discloses or suggests the use of  $\alpha$ -particles such as  $^{225}\text{Ac}$  and  $^{213}\text{Bi}$ . There is no explicit or implicit motivation to combine Turner. Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 17 of the Office Action, the Examiner rejected claim 28 as unpatentable over Macklis in view of van Geel, Kozak, and Turner. Applicant traverses the rejection. As

discussed above, the combination of Macklis, van Geel, and Kozak neither discloses all of the elements of the claims; nor is there a motivation to combine these references. Also discussed above, there is no motivation to further combine Turner. Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 18 of the Office Action, the Examiner rejected claim 29 as unpatentable over Macklis in view of van Geel, Kozak, and Zamora (USPN 5,443,816). Applicant traverses the rejection. As discussed above, the combination of Macklis, van Geel, and Kozak neither discloses all of the elements of the claims; nor is there a motivation to combine these references. In addition, there is no motivation to combine Zamora. Zamora is directed to radiolabeled peptides. However, Zamora is not directed to  $\alpha$ -particle radiolabeled peptides such as  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . For example, Zamora provides a long list of isotopes for use in its peptides, but does not mention or suggest  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . "Isotopes of the elements Tc, Re, and Cu are particularly applicable for use in diagnostic imaging and radiotherapy. The isotope  $^{99\text{m}}\text{Tc}$  is particularly applicable for use in diagnostic imaging. Other radionuclides with diagnostic or therapeutic applications include  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{97}\text{Ru}$ ,  $^{105}\text{Rh}$ ,  $^{109}\text{Pd}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{198}\text{Au}$ ,  $^{199}\text{Au}$ ,  $^{203}\text{Pb}$ ,  $^{211}\text{Pb}$  and  $^{212}\text{Bi}$ ." (See col. 11, ll. 52-64.) These radionuclides teach away from the present invention because none of these radionuclides are  $\alpha$ -particles that are suited for therapy against micrometastases of less than 1 mm in diameter. Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 19 of the Office Action, the Examiner rejected claim 41 under 35 U.S.C. 103(a) as unpatentable over Macklis in view of Gansow (USPN 4,454,106). Applicant traverses the rejection. The Examiner asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to modify Macklis with Gansow in order to provide  $^{213}\text{Bi}$ . Although  $^{213}\text{Bi}$  was reported by Gansow, it was merely provided in a laundry list of chelatable metals and alpha emitters. According to the Declaration of Dr. Scheinberg (see attached),  $^{213}\text{Bi}$  was never considered as a useful radiometal for therapeutic radioimmunoconjugates. It was not until Dr. Geerlings suggested the use of  $^{213}\text{Bi}$ , did Dr. Gansow and Dr. Scheinberg recognize  $^{213}\text{Bi}$  as a useful source of alpha radiation in a radioimmunoconjugate for therapy and that it

could be obtained easily and safely from  $^{225}\text{Ac}$ . (See attached copies of Declarations of Dr. Gansow and Dr. Scheinberg filed in reexaminations of USPNs 5,246,691 and 5,641,471.) Considering that it was unexpected at the time to use  $^{213}\text{Bi}$  for radioimmunoconjugate therapy, there is no motivation to combine a  $^{212}\text{Bi}$  reference such as Macklis with Gansow for the purpose of  $^{213}\text{Bi}$  teachings. Further, during reexamination, the claims in both USPN 5,246,691 and 5,641,471 overcame a 35 U.S.C. 103 rejection over Gansow (USPN 4,454,106). Therefore, applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 20 of the Office Action, the Examiner rejected claim 43 under 35 U.S.C. 103(a) as unpatentable over Macklis in view of Zamora. Applicant traverses the rejection. Claim 43 depends from claim 41. Claim 41 has been amended to specify that to the  $\alpha$ -particle emitting radioisotope is  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . Neither Macklis nor Zamora discloses  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . Neither Macklis nor Zamora disclose or suggest the use of  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$  in radioconjugates for therapy. As discussed herein, prior to the contributions of Dr. Geerlings, the state of the art focused on  $^{212}\text{Bi}$  for use in radioconjugates for therapy, not  $^{225}\text{Ac}$  or  $^{213}\text{Bi}$ . Thus, all of the elements of claim 43 are not disclosed or suggested by the combination of Macklis and Zamora. Applicant requests that the Examiner reconsider and withdraw this ground of rejection.

In § 22 of the Office Action, the Examiner rejected claims 26-29 and 39-43 under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. Patent No. 5,641,471. Although applicant believes the above-referenced claims are non-obvious over the claims in the cited patent, applicant stands ready to submit a terminal disclaimer to obviate the above-referenced obviousness-type double patenting rejections once the claims are deemed to be in condition for allowance. Until that time, applicant requests the Examiner to hold this rejection in abeyance.

In § 23 of the Office Action, the Examiner rejected claims 26-29 and 39-43 under the judicially created doctrine of obviousness-type double patenting over claims 1-11 and 20-22 of U.S. Patent No. 6,403,771. Although applicant believes the above-referenced claims are non-obvious over the claims in the cited patent, applicant stands ready to submit a terminal disclaimer

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to obviate the above-referenced obviousness-type double patenting rejections once the claims are deemed to be in condition for allowance. Until that time, applicant requests the Examiner to hold this rejection in abeyance.



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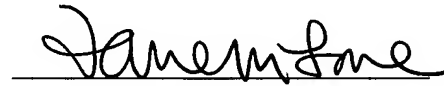
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### CONCLUSION

For the reasons stated above, we believe that all the pending claims are allowable and therefore ask the Examiner to allow them to issue.

Authorization is hereby given for a deduction for Deposit Account No. 08-0219 for the payment of a three-month extension of time. Please apply any charges that may be due, or any credits owed, to Deposit Account No. 08-0219.

Respectfully submitted,



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